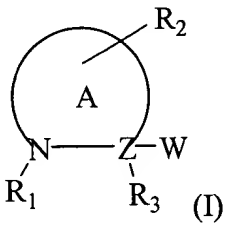
Amendments to the Specification:

Please amend the paragraph at page 9, line 5, as follows:

In other embodiments, the inhibitor is a non-peptidyl compound, e.g., which can be identified by such drug screening assays as described herein. These inhibitors can be, merely to illustrate, synthetic ~~organis~~organics, natural products, nucleic acids or carbohydrates.

In the claims:

1. (Currently Amended) A method for ~~modifying~~reducing the rate of ~~, in an animal,~~ metabolism of glucagon-like peptide 1 (GLP-1), comprising administering to ~~the~~ an animal a composition including one or more inhibitors of ~~a~~ dipeptidylpeptidase IV~~which inactivates GLP-1~~, wherein the inhibitor is represented by Formula I:



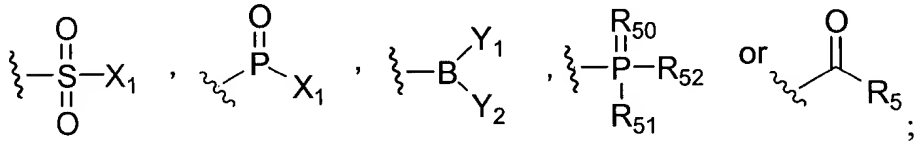
(I)

wherein

A represents a 4-8 membered heterocycle including the N and a Cα carbon;

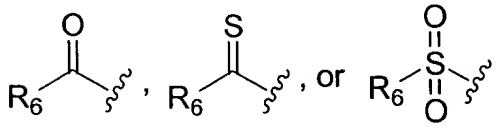
Z represents C or N;

W represents -CH=NR5, ~~a functional group which reacts with an active site residue of the targeted protease, or~~



;

R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C- terminally linked peptide or peptide analog, or an amino-protecting group, or



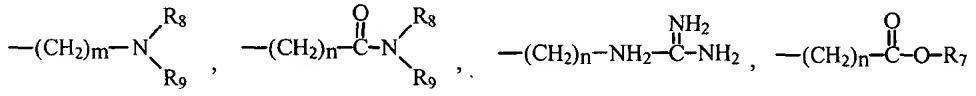
;

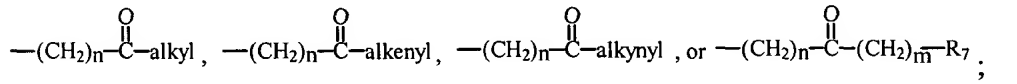
R_2 is absent or represents one or more substitutions to the ring A, each of which can independently be a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-lower alkyl, $-(CH_2)_m-S$-lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

if Z is N, R_3 represents hydrogen, if Z is C, R_3 represents hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-lower alkyl, $-(CH_2)_m-S$-lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

R_5 represents a hydrogen, an alkyl, an alkenyl, an alkynyl, $-C(X_1)(X_2)X_3$, $-(CH_2)_m-R_7$, $-(CH_2)_n-OH$, $-(CH_2)_n-O$-alkyl, $-(CH_2)_n-O$-alkenyl, $-(CH_2)_n-O$-alkynyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_n-SH$, $-(CH_2)_n-S$-alkyl, $-(CH_2)_n-S$-alkenyl, $-(CH_2)_n-S$-alkynyl, $-(CH_2)_n-S-(CH_2)_m-R_7$, $-C(O)C(O)NH_2$, or $-C(O)C(O)OR'_7$;

R_6 represents hydrogen, a halogen, ~~an~~ an alkyl, ~~an~~ an alkenyl, ~~an~~ an alkynyl, an aryl, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-alkyl, $-(CH_2)_m-O$-alkenyl, $-(CH_2)_m-O$-alkynyl, $-(CH_2)_m-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-alkyl, $-(CH_2)_m-S$-alkenyl, $-(CH_2)_m-S$-alkynyl, ~~or~~ $-(CH_2)_m-S-(CH_2)_m-R_7$,





R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle;

R'_7 represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, $-(CH_2)_m-R_7$, $-C(=O)$-alkyl, $-C(=O)$-alkenyl, $-C(=O)$-alkynyl, or $-C(=O)-(CH_2)_m-R_7$,

or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

R_{50} represents O or S;

R_{51} represents N_3, SH, NH_2, NO_2 or OR'7;

R_{52} represents hydrogen, a lower alkyl, an amine, OR'7, or a pharmaceutically acceptable salt, or R_{51} and R_{52} taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

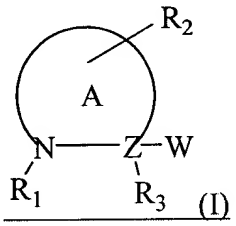
Y_1 and Y_2 can independently or together be a group capable of being hydrolyzed to a hydroxyl group, or cyclic derivatives where Y_1 and Y_2 are connected via a ring having from 5 to 8 atoms in the ring structure;

X_1 represents a halogen;

X_2 and X_3 each represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

2. (Currently Amended) A method for ~~modifying~~ improving glucose ~~metabolism of an animal~~tolerance, comprising administering to ~~the~~ an animal a composition including one or more protease inhibitors which inhibit ~~DPIV-mediated proteolysis~~dipeptidylpeptidase IV, wherein the inhibitor is represented by Formula I:



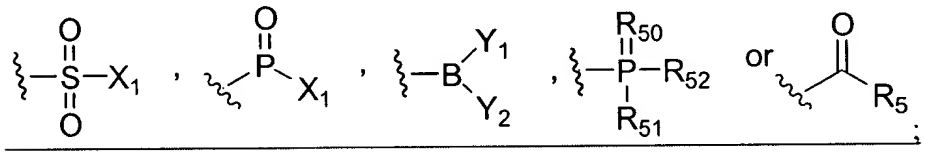
(I)

wherein

A represents a 4-8 membered heterocycle including the N and a Cα carbon;

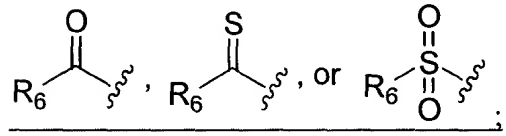
Z represents C or N;

W represents -CH=NR5,



;

R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C- terminally linked peptide or peptide analog, or an amino-protecting group, or



;

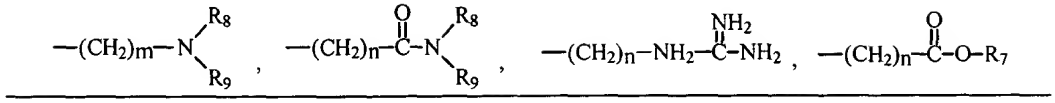
R_2 is absent or represents one or more substitutions to the ring A, each of which can independently be a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-lower alkyl, $-(CH_2)_m-S$-lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

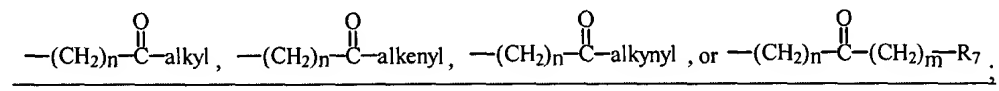
if Z is N, R_3 represents hydrogen, if Z is C, R_3 represents hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-lower alkyl, $-(CH_2)_m-S$-lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

R_5 represents a hydrogen, an alkyl, an alkenyl, an alkynyl, $-C(X_1)(X_2)X_3$, $-(CH_2)_m-R_7$, $-(CH_2)_n-OH$, $-(CH_2)_n-O$-alkyl, $-(CH_2)_n-O$-alkenyl, $-(CH_2)_n-O$-alkynyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_n-SH$, $-(CH_2)_n-S$-alkyl, $-(CH_2)_n-S$-alkenyl, $-(CH_2)_n-S$-alkynyl, $-(CH_2)_n-S-(CH_2)_m-R_7$, $-C(O)C(O)NH_2$, or $-C(O)C(O)OR'_7$;

R_6 represents hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-alkyl, $-(CH_2)_m-O$-alkenyl, $-(CH_2)_m-O$-alkynyl, $-(CH_2)_m-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-alkyl, $-(CH_2)_m-S$-alkenyl, $-(CH_2)_m-S$-alkynyl,

or -$(CH_2)_m$-S-$(CH_2)_m$-R_7,





R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle;

R'_7 represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, -$(CH_2)_m$-R_7, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, or -C(=O)-$(CH_2)_m$-R_7,

or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

R_{50} represents O or S;

R_{51} represents N_3, SH, NH_2, NO_2 or OR'_7;

R_{52} represents hydrogen, a lower alkyl, an amine, OR'_7, or a pharmaceutically acceptable salt, or R_{51} and R_{52} taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

Y_1 and Y_2 can independently or together be a group capable of being hydrolyzed to a hydroxyl group, or cyclic derivatives where Y_1 and Y_2 are connected via a ring having from 5 to 8 atoms in the ring structure;

X_1 represents a halogen;

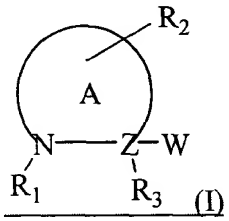
X_2 and X_3 each represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

3. (Currently Amended) ~~A~~ The method of claim 2, wherein said ~~for modifying glucose metabolism of an animal, comprising administering to the animal a composition including~~ one or more protease inhibitors ~~which inhibit the proteolysis of glucagon-like peptide 1 (GLP-1) and~~

~~accordingly~~ increase the plasma half-life of GLP-1 in the animal. ~~wherein the inhibitor is represented by Formula I~~

4. (Currently Amended) A method for treating Type II diabetes, comprising administering to an animal a composition including one or more inhibitors of dipeptidylpeptidase IV (DPIV) represented by Formula I:



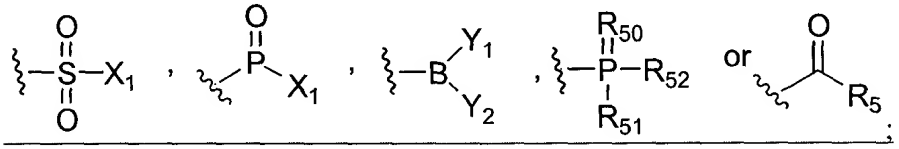
(I)

wherein

A represents a 4-8 membered heterocycle including the N and a Cα carbon;

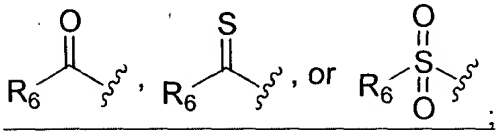
Z represents C or N;

W represents -CH=NR5,



;

R1 represents a C-terminally linked amino acid residue or amino acid analog, or a C- terminally linked peptide or peptide analog, or an amino-protecting group, or



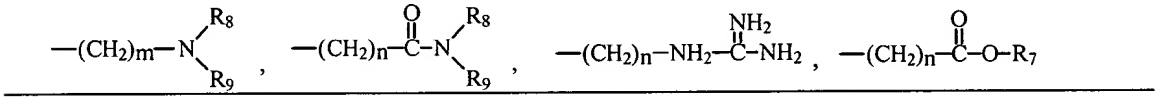
;

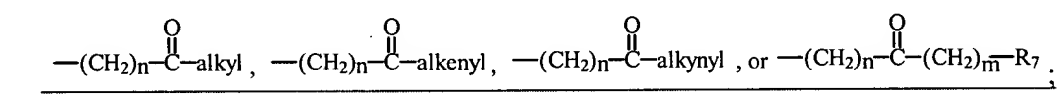
R2 is absent or represents one or more substitutions to the ring A, each of which can independently be a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, -$(CH_2)_m$-R7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-lower alkyl, -$(CH_2)_m$-O-lower alkenyl, -$(CH_2)_n$-O-$(CH_2)_m$-R7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-lower alkyl, -$(CH_2)_m$-S-lower alkenyl, or -$(CH_2)_n$-S-$(CH_2)_m$-R7;

if Z is N, R_3 represents hydrogen, if Z is C, R_3 represents hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-lower alkyl, $-(CH_2)_m-S$-lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

R_5 represents a hydrogen, an alkyl, an alkenyl, an alkynyl, $-C(X_1)(X_2)X_3$, $-(CH_2)_m-R_7$, $-(CH_2)_n-OH$, $-(CH_2)_n-O$-alkyl, $-(CH_2)_n-O$-alkenyl, $-(CH_2)_n-O$-alkynyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_n-SH$, $-(CH_2)_n-S$-alkyl, $-(CH_2)_n-S$-alkenyl, $-(CH_2)_n-S$-alkynyl, $-(CH_2)_n-S-(CH_2)_m-R_7$, $-C(O)C(O)NH_2$, or $-C(O)C(O)OR'_7$;

R_6 represents hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-alkyl, $-(CH_2)_m-O$-alkenyl, $-(CH_2)_m-O$-alkynyl, $-(CH_2)_m-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-alkyl, $-(CH_2)_m-S$-alkenyl, $-(CH_2)_m-S$-alkynyl, or $-(CH_2)_m-S-(CH_2)_m-R_7$,





R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle;

R'_7 represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, $-(CH_2)_m-R_7$, $-C(=O)$-alkyl, $-C(=O)$-alkenyl, $-C(=O)$-alkynyl, or $-C(=O)-(CH_2)_m-R_7$,

or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

R_{50} represents O or S;

R_{51} represents N_3, SH, NH_2, NO_2 or OR'$_7$;

R_{52} represents hydrogen, a lower alkyl, an amine, OR'$_7$, or a pharmaceutically acceptable salt, or R_{51} and R_{52} taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

Y_1 and Y_2 can independently or together be a group capable of being hydrolyzed to a hydroxyl group, or cyclic derivatives where Y_1 and Y_2 are connected via a ring having from 5 to 8 atoms in the ring structure;

X_1 represents a halogen;

X_2 and X_3 each represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

5. (Currently Amended) The method of claim 1 or 2, wherein the ~~dipeptidylpeptidase is DPIV~~animal is a mammal.

6. (Currently Amended) The method of claim ~~3~~5, wherein the ~~protease inhibitor is an inhibitor of DPIV~~mammal is a human.

7. (Currently Amended) The method of claim 2 or 3, wherein administering the inhibitor further reduces one or more of insulin resistance, glucose intolerance, hyperglycemia, hyperinsulinemia, obesity, hyperlipidemia, or hyperlipoproteinemia.

8. (Previously Presented) The method of claim 1, 2, 3 or 4, wherein the inhibitor has an EC_{50} for modification of glucose metabolism which is at least one order of magnitude less than its EC_{50} for immunosuppression.

9. (Currently Amended) The method of claim 1, 2, 3 or 4, wherein the inhibitor has an EC_{50} for inhibition of glucose intolerance in the nanomolar or less range.

10. (Currently Amended) The method of claim 8, wherein the inhibitor has an EC_{50} for immunosuppression in the ~~μM~~micromolar or greater range.

11. (Currently Amended) The method of claim 4, ~~5~~ or 6, wherein the inhibitor has a Ki for DPIV inhibition of 1.0 nM or less.

12. (Previously Presented) The method of claim 1, 2, 3 or 4, wherein the inhibitor is peptidomimetic of a peptide selected from Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala.

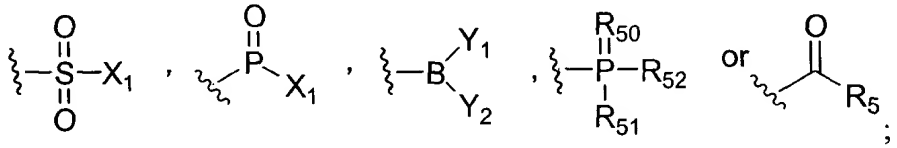
13. (Previously Presented) The method of claim 1, 2, 3 or 4, wherein the inhibitor has a molecular weight less than 7500 amu.

14. (Previously Presented) The method of claim 1, 2, 3 or 4, wherein the inhibitor is administered orally.

15. (Cancelled)

16. (Currently Amended) The method of claim 1, 2, 3, or 4, wherein

W represents $-CH=NR_5$,



;

R_5 represents H, an alkyl, an alkenyl, an alkynyl, $-C(X_1)(X_2)X_3$, $-(CH_2)m-R_7$, $-(CH_2)n-OH$, $-(CH_2)n-O-alkyl$, $-(CH_2)n-O-alkenyl$, $-(CH_2)n-O-alkynyl$, $-(CH_2)n-O-(CH_2)m-R_7$, $-(CH_2)n-SH$, $-(CH_2)n-S-alkyl$, $-(CH_2)n-S-alkenyl$, $-(CH_2)n-S-alkynyl$, $-(CH_2)n-S-(CH_2)m-R_7$, $-C(O)C(O)NH_2$, or $-C(O)C(O)OR'_7$;

R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R'_7 represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle;

Y_1 and Y_2 can independently or together be ~~OH, or~~ a group capable of being hydrolyzed to a hydroxyl group, ~~including~~ or cyclic derivatives where Y_1 and Y_2 are connected via a ring having from 5 to 8 atoms in the ring structure;

R_{50} represents O or S;

R_{51} represents N_3, SH, NH_2, NO_2 or OR'7;

R_{52} represents hydrogen, a lower alkyl, an amine, OR'7, or a pharmaceutically acceptable salt, or R_{51} and R_{52} taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

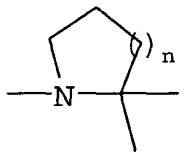
X_1 represents a halogen;

X_2 and X_3 each represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and

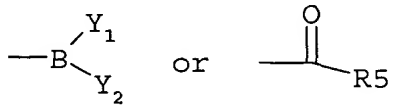
n is an integer in the range of 1 to 8.

17. (Previously Presented) The method of claim 16, wherein the ring A is represented by the formula:



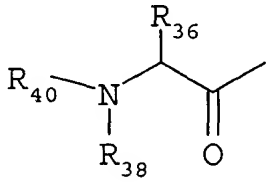
wherein n is an integer of 1 or 2.

18. (Previously Presented) The method of claim 16, wherein W represents



.

19. (Original) The method of claim 16, wherein R_1 represents



R_{36} is a small hydrophobic group and R_{38} is hydrogen, or, R_{36} and R_{38} together form a 4-7 membered heterocycle including the N and the Cα carbon, as defined for A above; and

R_{40} represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group.

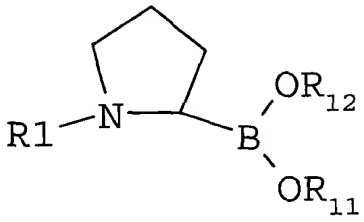
20. (Previously Presented) The method of claim 16, wherein R_2 is absent, or represents a small hydrophobic group.

21. (Previously Presented) The method of claim 16, wherein R_3 is a hydrogen, or a small hydrophobic group.

22. (Previously Presented) The method of claim 16, wherein R_5 is a hydrogen, or a halogenated lower alkyl.

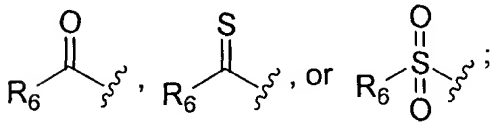
23. (Previously Presented) The method of claim 16, wherein X_1 is a fluorine, and X_2 and X_3, if halogens, are fluorine.

24. (Currently Amended) The method of claim 16, wherein the inhibitor is represented by the general formula:

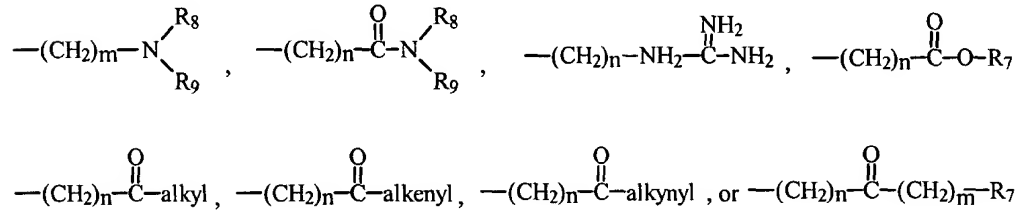


wherein

R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino protecting group, or



R_6 represents hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, -$(CH_2)_m$-R_7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-alkyl, -$(CH_2)_m$-O-alkenyl, -$(CH_2)_m$-O-alkynyl, -$(CH_2)_m$-O-$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-alkyl, -$(CH_2)_m$-S-alkenyl, -$(CH_2)_m$-S-alkynyl, -$(CH_2)_m$-S-$(CH_2)_m$-R_7,



R_7 represents an aryl, a cycloalkyl, a cycloalkenyl, or a heterocycle;

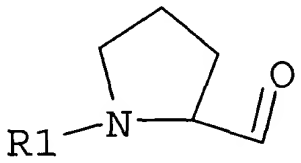
R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, -$(CH_2)_m$-R_7, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, or -C(=O)-$(CH_2)_m$-R_7,

or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

R_{11} and R_{12} each independently represent hydrogen, an alkyl, or a pharmaceutically acceptable salt, or R_{11} and R_{12} taken together with the O-B-O atoms to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

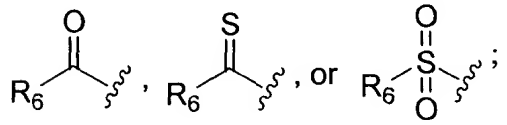
m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

25. (Currently Amended) The method of claim 16, wherein the inhibitor is represented by the general formula

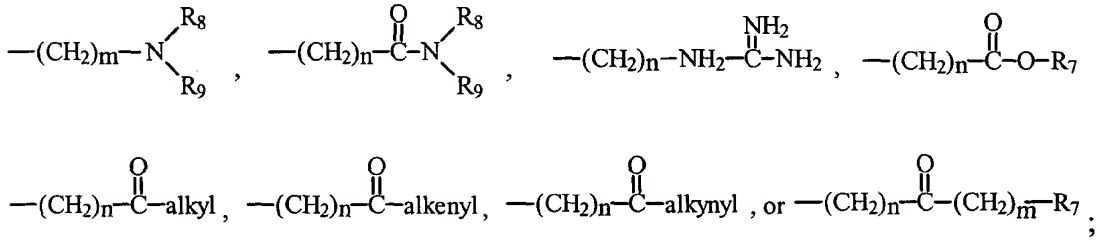


wherein

R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino protecting group, or



R_6 represents hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, -$(CH_2)_m$-R_7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-alkyl, -$(CH_2)_m$-O-alkenyl, -$(CH_2)_m$-O-alkynyl, -$(CH_2)_m$-O-$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-alkyl, -$(CH_2)_m$-S-alkenyl, -$(CH_2)_m$-S-alkynyl, -$(CH_2)_m$-S-$(CH_2)_m$-R_7,



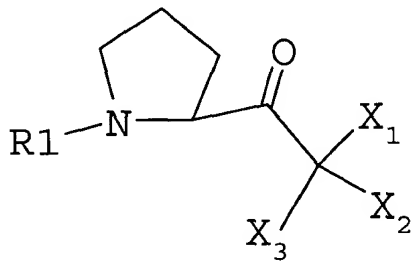
R_7 represents an aryl, a cycloalkyl, a cycloalkenyl, or a heterocycle;

R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, -$(CH_2)_m$-R_7, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, or -C(=O)-$(CH_2)_m$-R_7,

or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

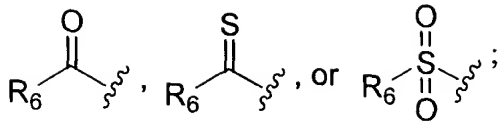
m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

26. (Currently Amended) The method of claim 16, wherein the inhibitor is represented by the general formula:

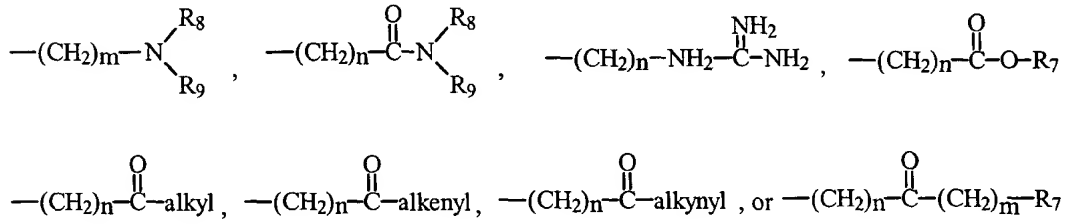


wherein

R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino protecting group, or



R_6 represents hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, -$(CH_2)_m$-R_7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-alkyl, -$(CH_2)_m$-O-alkenyl, -$(CH_2)_m$-O-alkynyl, -$(CH_2)_m$-O-$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-alkyl, -$(CH_2)_m$-S-alkenyl, -$(CH_2)_m$-S-alkynyl, -$(CH_2)_m$-S-$(CH_2)_m$-R_7,



R_7 represents an aryl, a cycloalkyl, a cycloalkenyl, or a heterocycle;

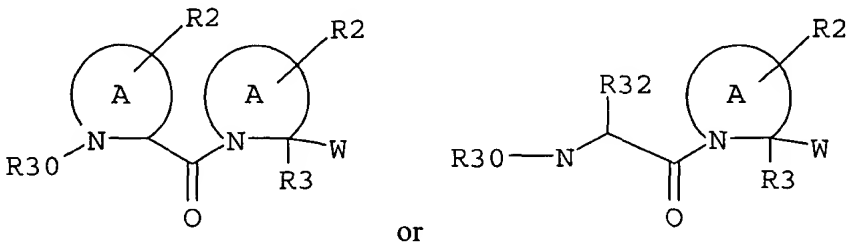
R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, -$(CH_2)_m$-R_7, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, or -C(=O)-$(CH_2)_m$-R_7,

or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

X_1, X_2 and X_3 each represent ~~a hydrogen or~~ a halogen;

m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

27. (Currently Amended) The method of claim 16, wherein the inhibitor is represented by the general formula:

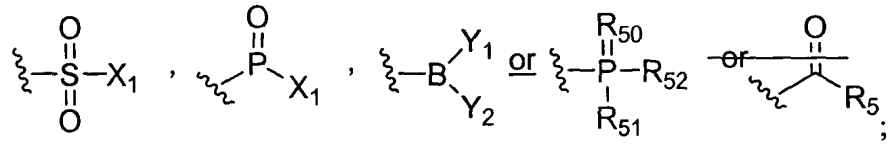


or

wherein

A represent a 4-8 membered heterocycle including an N and a Cα carbon;

W represents, ~~-CH=NR5;~~



R_2 is absent or represents one or more substitutions to the ring A, each of which can independently be a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-lower alkyl, $-(CH_2)_m-S$-lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

R_3 represents a hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-lower alkyl, $-(CH_2)_m-S$-lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

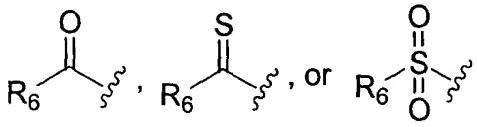
R_5 represents a hydrogen, an alkyl, an alkenyl, an alkynyl, $-C(X_1)(X_2)X_3$, $-(CH_2)_m-R_7$, $-(CH_2)_n-OH$, $-(CH_2)_n-O$-alkyl, $-(CH_2)_n-O$-alkenyl, $-(CH_2)_n-O$-alkynyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_n-SH$, $-(CH_2)_n-S$-alkyl, $-(CH_2)_n-S$-alkenyl, $-(CH_2)_n-S$-alkynyl, $-(CH_2)_n-S-(CH_2)_m-R_7$, $-C(O)C(O)NH_2$, or $-C(O)C(O)OR'_7$;

R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R'_7 represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R_{32} is a small hydrophobic group;

R_{30} represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group, or



R_{50} represents O or S;

R_{51} represents N_3, SH, NH_2, NO_2 or OR'7;

R_{52} represents hydrogen, a lower alkyl, an amine, OR'7, or a pharmaceutically acceptable salt, or R_{51} and R_{52} taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

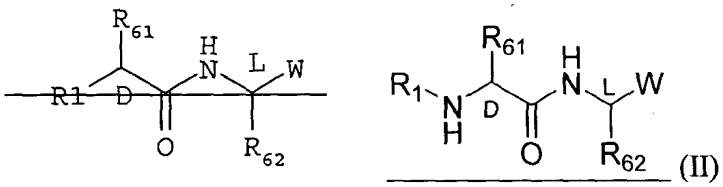
X_1 represents a halogen;

X_2 and X_3 each represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and

n is an integer in the range of 1 to 8.

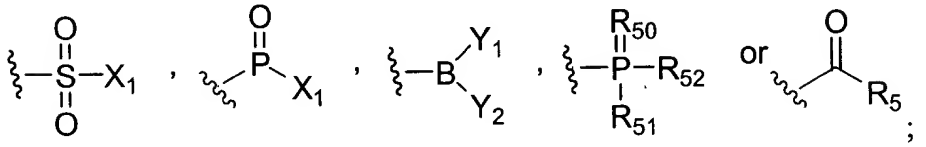
28. (Currently Amended) A method for modifying, in an animal, metabolism of glucagon-like peptide 1 (GLP-1), comprising administering to the animal a composition including one or more inhibitors of a dipeptidylpeptidase which inactivates GLP-1,, wherein the inhibitor is represented by Formula II:



(II)

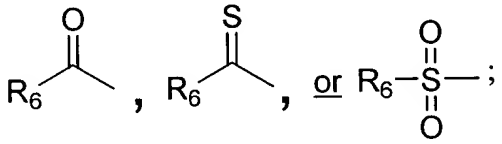
wherein

W represents a functional group which reacts with an active site residue of the targeted protease, selected from -CN, -CH=NR$_5$,



;

R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C- terminally linked peptide or peptide analog, or an amino-protecting group, or



;

R_3 represents hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, -$(CH_2)_m$-R_7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-lower alkyl, -$(CH_2)_m$-O-lower alkenyl, -$(CH_2)_n$-O-$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-lower alkyl, -$(CH_2)_m$-S-lower alkenyl, or -$(CH_2)_n$-S-$(CH_2)_m$-R_7;

R_5 represents H, an alkyl, an alkenyl, an alkynyl, -$C(X_1)(X_2)X_3$, -(CH_2)m-R_7, -(CH_2)n-OH, -(CH_2)n-O-alkyl, -(CH_2)n-O-alkenyl, -(CH_2)n-O-alkynyl, -(CH_2)n-O-(CH_2)m-R_7, -(CH_2)n-SH, -(CH_2)n-S-alkyl, -(CH_2)n-S-alkenyl, -(CH_2)n-S-alkynyl, -(CH_2)n-S-(CH_2)m-R_7, -C(O)C(O)NH_2, or -C(O)C(O)OR'$_7$;

R_6 represents hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, -$(CH_2)_m$-R_7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-alkyl, -$(CH_2)_m$-O-alkenyl, -$(CH_2)_m$-O-alkynyl, -$(CH_2)_m$-O-$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-alkyl, -$(CH_2)_m$-S-alkenyl, -$(CH_2)_m$-S-alkynyl, or -$(CH_2)_m$-S-$(CH_2)_m$-R_7;

R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle;

R'$_7$ represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle;

R_{61} and R_{62}, independently, represent small hydrophobic groups;

Y_1 and Y_2 can independently or together be OH, or a group capable of being hydrolyzed to a hydroxyl group, ~~including~~or cyclic derivatives where Y_1 and Y_2 are connected via a ring having from 5 to 8 atoms in the ring structure ;

R_{50} represents O or S;

R_{51} represents N_3, SH, NH_2, NO_2 or OR'7;

R_{52} represents hydrogen, a lower alkyl, an amine, OR'7, or a pharmaceutically acceptable salt, or R_{51} and R_{52} taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

X_1 represents a halogen;

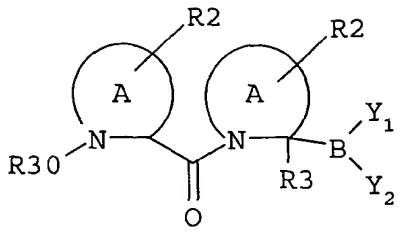
X_2 and X_3 each represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

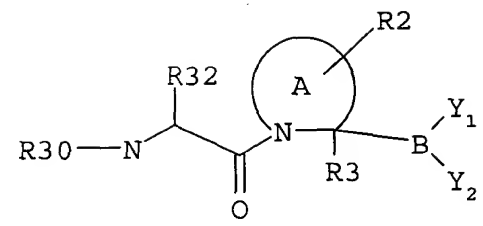
29. (Currently Amended) A method for ~~modifying~~modifying, in an animal, metabolism of peptide hormone, comprising administering to the animal a composition including one or more boronyl peptidomimetic inhibitors of dipeptidylpeptidase IV (DPIV) in an amount sufficient to increase the plasma half-life of a peptide hormone, which peptide hormone is selected from ~~the group consisting of~~ glucagon-like peptide 2 (GLP-2), growth hormone-releasing factor (GHRF), vasoactive intestinal peptide (VIP), peptide histidine isoleucine (PHI), pituitary adenylate cyclase activating peptide (PACAP), gastric inhibitory peptide (GIP), helodermin, Peptide YY and neuropeptide Y.

30. (Currently Amended) A method for modifying glucose metabolism of an animal, comprising administering to the animal a composition including a boronyl peptidomimetic of a peptide selected from Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala.

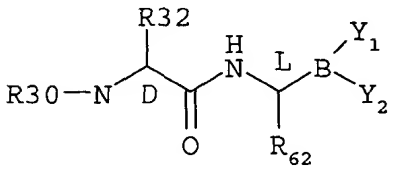
31. (Currently Amended) The method of claim ~~31~~30, wherein the boronyl peptidomimetic is represented in the general formula:



or



or



or

wherein

each A independently represents a 4-8 membered heterocycle including the N and a Cα carbon;

R_2 is absent or represents one or more substitutions to the ring A, each of which can independently be a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-lower alkyl, $-(CH_2)_m-S$-lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

R_3 represents hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-lower alkyl, $-(CH_2)_m-S$-lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

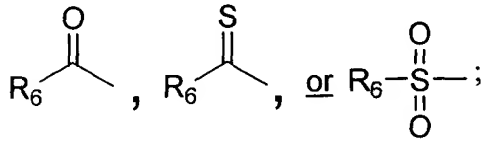
~~R_5 represents H, an alkyl, an alkenyl, an alkynyl, $-C(X_1)(X_2)X_3$, $-(CH_2)_m-R_7$, $-(CH_2)_n-OH$, $-(CH_2)_n-O$-alkyl, $-(CH_2)_n-O$-alkenyl, $-(CH_2)_n-O$-alkynyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_n-SH$, $-(CH_2)_n-S$-alkyl, $-(CH_2)_n-S$-alkenyl, $-(CH_2)_n-S$-alkynyl, $-(CH_2)_n-S-(CH_2)_m-R_7$, $-C(O)C(O)NH_2$, or $-C(O)C(O)OR'_7$;~~

R_6 represents hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-alkyl, $-(CH_2)_m-O$-alkenyl, $-(CH_2)_m-O$-alkynyl, $-(CH_2)_m-O-$

$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-alkyl, -$(CH_2)_m$-S-alkenyl, -$(CH_2)_m$-S-alkynyl, or -$(CH_2)_m$-S-$(CH_2)_m$-R_7;

R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle;

R_{30} represents a C-terminally linked amino acid residue or amino acid analog, or a C- terminally linked peptide or peptide analog, or an amino-protecting group, or



R_{32} and ~~R_{61}~~R_{62}, independently, represent small hydrophobic groups;

Y_1 and Y_2 can independently or together be OH, or a group capable of being hydrolyzed to a hydroxyl group, ~~including~~or cyclic derivatives where Y_1 and Y_2 are connected via a ring having from 5 to 8 atoms in the ring structure ;

m is zero or an integer in the range of 1 to 8; and n is an integer in the range of 1 to 8.

32. (Currently Amended) The method of claim 31, wherein administering the boronyl peptidomimetic reduces one or more of insulin resistance, glucose intolerance, hyperglycemia, hyperinsulinemia, obesity, hyperlipidemia, or hyperlipoproteinemia.

33. (Previously Presented) The method of claim 31, wherein the boronyl peptidomimetic has an EC_{50} for modification of glucose metabolism which is at least one order of magnitude less than its EC_{50} for immunosuppression.

34. (Previously Presented) The method of claim 31, wherein the boronyl peptidomimetic has an EC_{50} for inhibition of glucose tolerance in the nanomolar or less range.

35. (Previously Presented) The method of claim 31, wherein the boronyl peptidomimetic has an EC_{50} for immunosuppression in the μM or greater range.

36. (Previously Presented) The method of claim 31, wherein the boronyl peptidomimetic is administered orally.

37. (Currently Amended) A method for modifying glucose metabolism of an animal, comprising administering to the animal a composition comprising a peptidomimetic boronyl inhibitor wherein the peptide to be mimicked is Pro-Pro, Ala-Pro, ~~and~~ or (D)-Ala-(L)-Ala.

38. (New) The method of claim 6, wherein the human is a Type II diabetic.

39. (New) The method of claim 14, wherein the inhibitor is administered in a single dosage.

40. (New) The method of claim 39, wherein the total daily dosage of the inhibitor is less than 2000 mg.

REMARKS

Claims 1-14 and 16-40 constitute the pending claims in the present application. Issues raised by the Examiner will be addressed below in the order they appear in the Advisory Action mailed on May 22, 2003, and the Final Office Action mailed November 12, 2003. Applicants are concurrently filing with this Preliminary Amendment a Request for Continued Examination. Applicants reiterate herein the amendments and remarks they submitted in their response to the Final Office Action filed on May 14, 2003. This Preliminary Amendment further includes additional corrections and remarks addressing new issues raised in the Advisory Action. To avoid confusion as to which amendments to enter and which remarks to consider, Applicants respectfully request that the Examiner disregard unentered amendments and enter the amendments and consider the remarks presented herein (in this Preliminary Amendment). Applicants respectfully request reconsideration in view of the following remarks.

Response to issues the Examiner raised in the Final Office Action mailed on November 12, 2002

1. Applicants have added the phrase "boronyl peptidomimetic" before the term "inhibitor" in claim 29.

2. Applicants have herein corrected the misspelling of the term "organics" on page 9, line 6 of the specification.

3. Claims 2-4, 6-14, 16-23, 28, and 31-37 are rejected under 35 U.S.C. 112, second paragraph.

a. Claims 2-4 are deemed indefinite because they do not explicitly recite what constitutes Formula 1. Applicants have herein explicitly defined Formula 1 for claims 2-4. Applicants assert that the amendments do not narrow the scope of the claims.

b. Applicants have removed the term "including" from claims 16, 28 and 31. Applicants assert that the amendments do not narrow the scope of the claims.

c. Applicants corrected the structural formula in claim 28. Applicants submit that the previous structure was an obvious error, that one skilled in the art would have recognized that the structure as amended was what was intended in the first place. Applicants respectfully submit that the amended structure renders moot the concerns raised in the Office Action.

d. Applicants have herein corrected the dependency of claim 31. Applicants assert that the amendment does not narrow the scope of the claim.

e. Applicants have removed variables R_5 and R_{61} from claim 31. Applicants assert that the amendment does not narrow the scope of the claim.

f. Applicants removal of the variable R_5 from Claim 31 renders moot the need to define R'_7.

g. Applicants have herein defined variable R_{62} for claim 31. Applicants assert that the amendment in no way narrows the scope of the claim.

h. Applicants have changed the term "and" to "or" in claim 37. Applicants assert that the amendment in no way narrows the scope of the claim.

Applicants appreciate the Examiner pointing out the informalities which Applicants have corrected above. Applicants assert that the claims are definite as amended. Applicants also assert that a skilled artisan would have recognized the informalities and the required corrections. As such, submit that a skilled artisan would not have been confused as to the scope of the claims.

5. Claims 1-14, 16-26, 28, and 30-36 are objected to for containing informalities. Applicants address each informality in the order that it is presented in the Office Action.

a. Applicants have herein removed the underlining on claim 1 of the amendment filed September 16, 2002. Applicants assert that the amendment does not narrow the scope of the claim.

b. Applicants have herein removed "or" from claim 1, page 6, line 10, of the amendment filed September 16, 2002. Applicants assert that the amendment does not narrow the scope of the claim.

c. Applicants have herein added a period at the end of claim 9. Applicants assert that the amendment does not narrow the scope of the claim.

d. Applicants have herein inserted an "or" at claim 24, page 11, line 9; claim 25, page 12, line 9, claim 26, page 13, line 10; claim 28, page 16, line 4; and claim 31, page 19, line 7. Applicants assert that the amendments do not narrow the scope of the claims.

e. Applicants have herein changed first occurrence of "a" to "an" at claim 24, page 11, line 12. Applicants assert that the amendment does not narrow the scope of the claim.

f. Applicants have herein inserted a semicolon at the end of the line at claim 28, page 17, line 8. Applicants assert that the amendment does not narrow the scope of the claim.

g. Applicants have herein inserted an "a" after "including" at claim 30, line 2. Applicants assert that the amendment does not narrow the scope of the claim.

h. Applicants have herein inserted an "or" before "hyperlipoproteinemia" at claim 32, line 2. Applicants assert that the amendment does not narrow the scope of the claim.

Applicants appreciate the Examiner pointing out the informalities which Applicants have corrected above. Applicants also assert that a skilled artisan would have recognized the informalities and the required corrections. As such, submit that a skilled artisan would not have been confused as to the scope of the claims.

6. Claim 26 is objected to under 37 C.F.R. 1.75(c) as being of improper dependency. Applicants have amended the claim to remove hydrogen from the definition of X_1 in claim 26. Applicants submit that the amended claim is of proper dependent form. Accordingly, Applicants respectfully request removal of the rejection.

7. Claims 1-14 and 16-37 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-67 of co-pending Application No. 09/628,225. The Office Action further stated that "[A]lthough the conflicting claims are not identical, they are not patently distinct from each other because the claims of the '225 application anticipate the instant claims." Applicants traverse the rejection to the extent it is

maintained over the amendments. Applicants will address the issue at a later time, should it be maintained.

8. Applicants note with appreciation that rejections based on the Deacon et al. and WO Patent Application 98/25644 have been removed on account of the priority data of the instant application.

9. Claims 1-3, 5-13, 16, 20, 21, 25, and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application '309. Applicants respectfully traverse the rejection.

Claims 1-4, and 29 are the independent claims in the rejected claim set. Claims 5-13, 16, 20, 21, and 25 ultimately depend from claims 1, 2, 3, or 4. Thus, if claims 1-4 are shown to be novel, then novelty inheres to the dependent claims.

Applicants reiterate their arguments from the previous response. Applicants assert that the instant claims are not anticipated by the '309 application. While the '309 application claims DPIV inhibitors, it does not disclose every element of the amended pending claims. The '309 application discloses that inhibition of DPIV inhibitors may be useful as immunosuppresants, prevention drugs for HIV infection of $CD4^+$ T-cells, preventions drugs for progression metastaeses, for treating psoriatic or arthritic conditions, for treating prostate hypertrophy, or for suppression of sperm motility. (See page 3 of '309 app) Thus, the '309 application does not teach or suggest that DPIV inhibitors can be used to modify glucose tolerance and/or GLP-1 metabolism in vivo, nor does the Examiner point to facts in the art that would bridge that gap. As such the instant claims are directed to new and unobvious uses of DPIV inhibitors not disclosed in the 309 application.

Applicants further reiterate their arguments regarding In re Marshall. The fact that glucose tolerance and/or GLP-1 metabolism might have been modified to the same extent in the experiments described in the '309 application is not relevant because, for inherent anticipation of **method claims**, if a claimed method comprises steps identical to those of a method practiced in the prior art, and the same result would have been achieved in the prior art method, the accidental or unwitting achievement of that result cannot constitute anticipation. *In re Marshall*, 578 F.2d 301, 198 USPQ 344 (CCPA 1978). In *Marshall* the PTO board used the *Physician's*

Desk Reference (PDR) as a basis for a rejection of the applicant's weight control process. The applicant's process involved anesthetizing certain intestinal nerve ends receptors with oxethazaine. The anesthesia inhibited the release of certain appetite simulating hormones thereby inhibiting appetite. The PDR had disclosed that oxethazaine inhibits the release of gastrointestinal hormones, and such inhibition would be useful for treating certain gastrointestinal ailments. In reversing the Board's rejection, the court held that the PDR did not teach the use of the compound as a weight control drug. Addressing the issue of inherency, the court further stated that "[I]f anyone ever lost weight by following the PDR teachings it was an unrecognized accident. An accidental or unwitting duplication of an invention cannot constitute an anticipation." (*id.* 304)

Applicants maintain that *Marshall* is controlling in the instant situation. In *Marshall*, note that the essential question with regards to inherency was not whether oxethazaine had inhibited the release of intestinal hormones in patients prior to the applicant's weight control process, or whether patients had lost weight when oxethazaine was administered to them as an anesthetic. Rather the question was whether the prior reference taught the reader that weight loss can be achieved by using oxathazine. Thus, if the 102 reference does not teach or suggest the claimed process, then the claimed process is new and unobvious in view of the reference.

The instant claims, as amended, are directed to uses of DPIV inhibitors to improve glucose tolerance and/or decrease GLP-1 metabolism in an animal. Applicants point out that the MPEP does not foreclose patentability where "new and unobvious uses of old structures and compositions" are present (MPEP 2112.02, original emphasis) Under *Marshall*, "accidental or unwitting duplication of an invention cannot constitute an anticipation." (*Marshall*, 578 F.2d at 304) Thus, to sustain an anticipation by inherency, the '309 application must teach or suggest the benefits of modifying GLP-1 metabolism in a manner that is not accidental or unwitting. One of ordinary skill in the art, having read the '309 application, should be able to achieve therapeutic benefits by modifying GLP-1 metabolism. The '309 application lists six pharmaceutical applications of the DPIV inhibitors discloses therein: (1) immunosuppression, (2) HIV prevention and AIDs treatment, (3) prevention of breast and prostate tumor metastases into the lungs, (4) treatment of dermatological diseases such as psoriasis, (5) suppression of sperm motility to achieve male contraception, and (6) treatment of benign prostate hypertrophy. (See

'309 application, p. 3) Applicants point out that none of the six enumerated uses relate to glucose tolerance or GLP-1 metabolism. The '309 application was not seeking to improve glucose tolerance, it did not monitor the effects the DPIV inhibitors had on glucose tolerance, nor is there any suggestion that glucose tolerance was related to the therapeutic uses enumerated in the '309 application. To the best of Applicants' knowledge, GLP-1 is not related to the therapeutic uses enumerated in the '309 application. Applicants urge that one of ordinary skill in the art, having read the '309 application, would not have known to use DPIV inhibitors to improve glucose tolerance and/or decrease GLP-1 metabolism in vivo for therapeutic purposes.

The only biological testing carried out in the '309 application were *in vitro* assays using purified human DPIV. (See '309 application, page 9) There is no indication that any GLP-1 enzyme was even present in the preparation. The experiments disclosed in the '309 application neither show what effects the disclosed inhibitors had on glucose tolerance, nor do they show any beneficial therapeutic uses arising from modifying GLP-1 metabolism. Applicants assert that one of ordinary skill in the art would have been hard pressed to find even a teaching or suggestion that the DPIV inhibitors could achieve beneficial uses by modifying GLP-1 metabolism. Thus, Applicants assert that an inherency rejection cannot be sustained based on the '309 application. Accordingly, Applicants respectfully request reconsideration and removal of the rejection.

The Office Action stated that *Marshall* does not represent the current state of the law with respect to inherency and anticipation rejections, and offered the following citations from the MPEP 2112 and 2112.02, *Ex parte Novitski*, 26 USPQ2d 1389, 1391 (BPAI 1993), *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1548, 220 USPQ 303, 309 (Fed. Cir. 1983) cert. denied, 469 U.S. 851 (1984) and *Abbott Labs. v. Geneva Pharms., Inc.*, 182 F.3d 1315, 1319, 51 USPQ2d 1307, 1309 (Fed. Cir. 1999), cert. denied, 528 U.S. 1078 (2000). Applicants assert that the cases cited in the Office Action do not overrule *Marshall*, and are not in conflict with *Marshall*. Applicants assert that anticipation is a complex legal field encompassing on-sale bar, public use and various common law exceptions. New cases may arise to address different aspects of anticipation. Indeed, the cases cited by in the Office Action may reflect the efforts various courts to address aspects of anticipation. Applicants argue, however, the appearance of new cases which do not overrule or narrow the older cases, does not reduce the controlling force

of the older cases. Applicants assert that Marshall is still good law even in view of the cases cited in the Office Action. The Federal Circuit in 1990 cited *Marshall* approvingly acknowledging patentability of method claims when an applicant discovers a completely new use for an old compound. (See *In re Woodruff*, 919 F.2d 1575, 1578) Moreover, the "accidental or unwitting duplication test" of *Marshall* has been applied as recently as 1998 in *Mehl/Biophile Int'l Corp v. Milgraum*, 8 F. Supp.2d 434, 447.

Applicants further assert that *Marshall* is not in conflict with the *Abbot* decision cited in the Office Action because the two opinions relate to anticipation in different contexts. The Office Action stated that under *Abbot Labs. v. Geneva Pharms., Inc.*, 182 F.3d 1315, the "accidental and unwitting cases" are only applicable when the claimed invention is "anticipated by earlier work that produced no useful or appreciated result." (See Abbot Labs, at 1319) Applicants assert that *Abbot* is not conflict with *Marshall*. Specifically, *Marshall* deals with anticipation in the **method claim** context, while Abbot deals with anticipation in the **on-sale bar** context. This distinction is important because, *Abbot* did not involve a new use for an old compound. Applicants argue that the Fed. Cir. in *Abbot* did not mean to foreclose patentability of a claimed invention by an earlier work just because the earlier work produced something useful or appreciated regardless of whether elements of the claimed invention contributed to the usefulness of the product, or if what is appreciated about the product are the elements in the claimed invention. Such an interpretation would be problematic and inapposite with the language and understanding of MPEP 2112 and 2112.02 which does not foreclose patentability in cases where old structures and compositions are used in "new and unobvious uses." (See MPEP 2112.02) Rather, the Federal Circuit held that anticipation of a claimed invention would be sustained only when the useful and appreciated results of the earlier work are attributable to the elements disclosed in the claimed invention. In *Abbot* the court determined the sale of a batch crystalline polymorph one year prior to Abbot's patent application for one of the polymorphs posed an on-sale bar regardless of whether the seller or buyer knew that the product sold had the claimed characteristics. The court correctly found anticipation because the sold samples consisted of the claimed polymorph, the samples had pharmaceutical use, and the use was attributable to the claimed polymorph. Thus *Abbot* was not addressing an "accidental and unwitting" case within the *Marshall* context.

Whereas *Abbot* did not fall in the "accidental and unwitting" category, Applicants assert the instant situation falls squarely within *Marshall*. In the present case, the cited earlier work was directed to uses that are different than the claimed methods, i.e., the inventors assert that they are affecting a different biological process. The Office Action has not presented any evidence that the underlying success and usefulness of the earlier works is attributable to modification of GLP-1 metabolism in vivo. Thus the cited earlier works do not inherently anticipate the instant method claims.

10. Claims 1-3, 5-13, 16-24, 26, 27, 29-35 and 37 U.S.C. 102(b) as being anticipated by the WO Patent Application '259. Applicants traverse the rejection to the extent it is maintained over the amended claims.

Applicants reiterate their previous arguments. To anticipate a claim, the reference must teach every element of the claim. (MPEP 2131) While the '259 application makes composition of matter claims of DPIV inhibitors, it does not disclose every material element of the claimed subject matter of the instant application because it does not teach or suggest that DPIV inhibitors can be used to improve glucose tolerance or decrease GLP-1 metabolism in vivo. As above, If the Examiner continues to rely on rejecting the pending claims as being anticipated by the '259 application, Applicants respectfully request that the factual basis, including that which overcomes the mere anticipated inherency [if at all], be clearly articulated. Any modulation of GLP-1 metabolism in the experiments described in the '259 application would have been an unrecognized accident, and thus cannot constitute inherent anticipation of the instant claims. Therefore, Applicants respectfully request reconsideration of this rejection.

11. Claims 1-14, and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Villhauer. The Office action stated that "since the same active agents are being administered to the same animals according to the same method steps, inherently peptide hormone metabolism will be modified t the same extent in the method of Villhauer as is claimed by Applicants." Applicants respectfully traverse the rejection to the extent it is maintained over the amended claims.

Applicants assert that Villhauer does not disclose the compounds in the instant claims as amended. To anticipate a claim, the reference must teach every element of the claim. (MPEP

2131) Applicants have cancelled claim 15. To the extent the subject matter of claim 15 appears in other claims, namely claims 1-4, Applicants have amended the claims such that the compounds in the instant claims are not within the scope of the compounds disclosed by Villhauer. Note in particular that all of Villihauer's compounds contain a prolyl residue wherein the carboxyl moiety has been replaced by a cyano group. In amended claims 1-4 and claims dependent thereon, Applicants have removed a cyano group from being one of the possibilities for W. Therefore, Applicants assert that the compounds in the instant amended claims 1-4, and the claims dependent thereon, are not the same as Villihauer's compounds. Thus, Villhauer does not disclose all the limitations of the instant claims. Accordingly, Applicants respectfully request reconsideration and removal of the rejection.

21. Claims 29 is rejected under 35 U.S.C. 102(b) as being anticipated by the German Patent 19 61 6486. Applicants traverse the rejection to the extent it is maintained over the amended claims.

Applicants have amended claim 29 so that the claim is drawn to boronyl peptidomimetic inhibitors of dipeptidyl peptidase IV. Applicants assert that the '486 patent does not disclose boronyl peptidomimetic inhibitors of dipeptidyl peptidase IV. As such, Applicants submit that the '486 patent fails to anticipate 29 because it does not disclose every limitation of the claims. Therefore, Applicants respectfully request reconsideration and removal of the rejection.

Response to issues the Examiner raised in the Advisory Action mailed on May 22, 2003

1a. The Advisory Action noted that the amendments to the specification presented in Applicants response filed on May 14, 2003, were not entered because they were not presented in a proper format. Applicants have herein presented the amendment to the specification in a correct format.

1b. The Advisory Action noted that the text to be added to claim 4 (page 9, line 15) was not underlined. Applicants have herein underlined the text in claim 4. Applicants have also underlined a similar addition presented in claim 2.

1c. The Advisory Action noted that claim 11 was presented as previously amended while containing a strike-out. Applicants have correctly identified herein that claim 11 is presently amended.

2a. The Advisory Action noted that the word "reducing" in claim 1 is misspelled. Applicants have herein corrected the misspelling.

2b. The Advisory Action noted that the proposed amendment to the preamble of claim 2 ("improving glucose tolerance") raises new issues under 35 U.S.C. 112, 2nd paragraph, with respect to claim 7 ("reduces...glucose tolerance"). Applicants have amended claim 7 to indicate that the effects enumerated in claim 7 are additionally specified results of practicing the method in claim 2.

2c. The Advisory Action noted that the proposed amendment to claim 28 raises new issues requiring further consideration. Applicants acknowledge the Examiner's assessment, but reiterate that the proposed amendment does not raise new matter, in that a skilled person, in light of the specification, would have identified the error in Formula II of claim 28, and would have recognized the obvious correction as being the proposed amendment.

3. The Advisory Action noted that the proposed amendments filed May 14, 2003, did not address corrections, i.e., insertion of "or", to claim 28 (page 16, line 4) and claim 31 (page 19, line 7). Applicants have herein provided the requested corrections. Applicants assert that these corrections do not narrow the scope of the claim.

4. Applicants will address the provisional obviousness-type double patenting rejection when the rejection is no longer provisional.

5a. The Advisory Action maintained the rejection over WO Patent Application '309 and WO Patent Application '259. Applicants reiterate the arguments presented in the response filed on May 14, 2003. Additionally, Applicants direct the Examiner's attention to a recent Federal Circuit case, Janssen v. Rexall, 03-1069, (decided September 8, 2003). There the Federal Circuit held that practicing a method of treatment claim requires as an element intending to treat the recited condition. Accordingly, anticipating a method of treatment claim likewise would require disclosure of the intent to treat, i.e., the administration of a compound must be done with intent

to achieve the intended result of the claimed invention. In this case, neither the '259, nor the '309 applications teach administering compounds to reduce the rate of GLP-1 metabolism, to improve glucose tolerance, to treat Type II diabetes, or to reduce one or more of insulin resistance, glucose intolerance, hyperglycemia, hyperinsulinemia, obesity, hyperlipidemia, or hyperlipoproteinemia. Thus, the cited references do not anticipate the instant claims as a matter of law. Accordingly, Applicants respectfully request reconsideration and removal of the rejections.

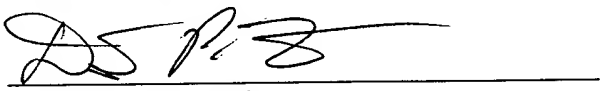
5b. Applicants note with appreciation that the proposed amendments filed May 14, 2003, would have overcome the rejections over Villhauer and German Patent '486.

5c. Applicants note with appreciation that the proposed claim 38 would be novel and unobvious over the prior art of record. Applicants acknowledge, however, that this claim would be subject to the same provisional obviousness-type double patenting rejection set forth in the Final Office Action. Applicants will address this issue when it is no longer provisional.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,



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